PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/053620	International filing date *(day/month/year)* 20.12.2004
Priority date *(day/month/year)* 18.12.2003	
International Patent Classification (IPC) or both national classification and IPC C07D401/06, A61K31/4184, C07D413/14, A61P11/00, A61P31/12	
Applicant TIBOTEC PHARMACEUTICALS LTD.	

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Lauro, P

Telephone No. +49 89 2399-8288

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/053620

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-32
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/053620

Re Item V

1. The following documents are referred to:

D1: WO 01/00615 A (JANSSENS FRANS EDUARD ;ANDRIES KOENRAAD JOZEF LODENWI (BE); JANSSE) 4 January 2001 (2001-01-04)
D2: WO 01/00612 A (JANSSENS FRANS EDUARD ;SOMMEN FRANCOIS MARIA (BE); ANDRIES KOENRAA) 4 January 2001 (2001-01-04)
D3: WO 01/00611 A (JANSSENS FRANS EDUARD ;SOMMEN FRANCOIS MARIA (BE); ANDRIES KOENRAA) 4 January 2001 (2001-01-04)
D4: JANSSENS F ET AL: "NEW ANTIHISTAMINE N-HETEROCYCLIC 4-PIPERIDINAMINES. 2. SYNTHESIS AND ANTIHISTAMINIC ACTIVITY OF 1-(4-FLUOROPHENYL)METHYL-N- (4-PIPERIDINYL)-1H-BENZIMIDAZOL-2-AMINES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 28, no. 12, December 1985 (1985-12), pages 1934-1943, XP000881979 ISSN: 0022-2623

2. **Novelty**
The compounds claimed in claim 1 of the present application differ from the compounds disclosed in D1 to D3, in the nature of the substituent at the 2-position of the benzimidazole ring. The compound no. 8 disclosed in D4 lacks a substituent on the benzo fused part of the benzimidazole ring. Novelty re D1 to D4 is acknowledged.

3. **Inventive step**
The problem underlying the present application appears to reside in the provision of benzimidazole derivatives useful in the respiratory syncytial virus (RSV) replication inhibitors.

Benzimidazole derivatives with the same activity are disclosed in D1 to D3. As outlined above, the difference with respect to the exemplified compounds in the cited prior art resides in the nature of the 2-substituent. However, in the generic definition of the formula claimed in the respective claim 1 in D1 to D3, the benzimidazole may be substituted at the 2-position with a variety of groups which may contain piperidinyl, pyrrolidinyl groups variably substituted. Since the compounds of the current

application appear to have structural features which are to be considered equivalent to those disclosed in D1 to D3, they would have been expected to possess the alleged activity. In the absence of data which show that the compounds of the present application have unexpected effects compared to the structurally closest compounds disclosed in the cited prior art, inventive step cannot be acknowledged.

4. The inclusion of the prodrug form of the compounds of formula I in the claims is not acceptable, since it is not clear where the compounds may be derivatized and which are the groups supposed to be sufficiently labile in vivo to ensure a sufficiently high rate and extent of conversion.